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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 21 JUN 2005
WIPO PCT

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
1626 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/005265	23.02.2004	24.02.2003

International Patent Classification (IPC) or national classification and IPC
C07C319/20, C07C148/00, C07C149/273, C07C323/60

Applicant
MALLINCKRODT INC. et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.12.2004	17.06.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/005265

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-12 as originally filed

   Claims, Numbers

   1-34 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 14-34

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 14-34

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-13 .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4,5,10,11
	No:	Claims	1-3,6-9,12,13
Inventive step (IS)	Yes:	Claims	
	No:	Claims	4,5,10,11
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Re Item IV

Lack of unity of invention

D1: US 2004/002547 A1 (LARGEAU DENIS ET AL) 1 January 2004 (2004-01-01)

D2: EP-A-1 260 501 (CHEMAGIS LTD) 27 November 2002 (2002-11-27)

D3: WO 02/10125 A (GERSHON NEOMI ; SINGER CLAUDE (IL); TEVA PHARMA (IL); ARONHIME JUDITH) 7 February 2002 (2002-02-07)

D4: US-A-4 177 290 (LAFON LOUIS) 4 December 1979 (1979-12-04)

1. The present application does not fulfill the requirements of Rule 13 PCT, the reason being that the present patent application relates to three inventions, namely:

1. Claims 1-13

Process for preparing benzhydrylthioacetamide comprising reacting benzhydrylthiocarboxamidine salt with haloacetamide in a reaction medium comprising water, a water miscible organic solvent and a water soluble basic salt.

2. Claims 14-25

Process for preparing modafinil comprising: a) reacting benzhydrol with thiourea in the presence of hydrogen bromide to provide benzhydrylthiocarboxamidine bromide, b) reacting haloacetamide with the product of step a) to provide benzhydrylthioacetamide and c) oxidizing the product of step b) to obtain benzhydrylsulphinylacetamide wherein the reaction of step b) is conducted in a solvent comprising a water miscible organic solvent and water in the presence of a basic salt.

3. Claims 26-34

Process for the purification of modafinil which comprises contacting the crude modafinil with a halo-organic solvent and then separating the modafinil from the solvent.

2. A situation of lack of unity has been found. The reasons are the following:

Modafinil, its production and its purification are known in the state of the art (D2-D4). Furthermore, processes for preparing benzhydrylthioacetamide comprising reacting benzhydrylthiocarboxamidine salt with haloacetamide in a reaction medium comprising water, a water miscible organic solvent and a water soluble basic salt are known as well (D2). Consequently there is not a common technical feature which can be regarded as a special technical feature in the sense of Rule 13.1 PCT and which links the different inventions. Hence, the present application is not unitarian.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The first invention, claims 1-13, relates to a process for preparing benzhydrylthioacetamide comprising reacting benzhydrylthiocarboxamidine salt with haloacetamide in a reaction medium comprising water, a water miscible organic solvent and a water soluble basic salt.

2. D1 discloses a process for preparing modafinil comprising: a) reacting benzhydrol with thiourea in the presence of hydrogen bromide to provide benzhydrylthiocarboxamidine bromide, b) reacting haloacetamide with the product of step a) to provide benzhydrylthioacetamide and c) oxidizing the product of step b) to obtain benzhydrylsulphinylacetamide wherein the reaction of step b) is conducted in a solvent comprising a water miscible organic solvent and water in the presence of a basic salt.

3. D2 discloses a process for preparing modafinil comprising: a) reacting benzhydrol with thiourea in the presence of hydrogen bromide to provide benzhydrylthiocarboxamidine bromide, b) reacting haloacetamide with the product of step a) to provide benzhydrylthioacetamide and c) oxidizing the product of step b) to obtain benzhydrylsulphinylacetamide wherein the reaction of step b) is conducted in a solvent comprising a water miscible organic solvent such an alcohol and water in the presence of a basic salt such as an alkali metal hydroxide.

4. D3 discloses a process for the purification of modafinil comprising contacting the

crude modafinil with a solvent.

5. D4 discloses a process for the production of modafinil by reaction of benzhydrylthioacetic acid with thionyl chloride leading to benzhydrylthioacetyl chloride which reacts afterwards with ammonia leading to benzhydrylthioacetamide which is afterwards oxidized to benzhydrylsulphinylacetamide, modafinil.

Novelty

6. The subject-matter of claims 1-3, 6-9, 12 and 13 is not novel in the sense of Art. 33(2) PCT. D2 discloses a process for preparing modafinil comprising: a) reacting benzhydrol with thiourea in the presence of hydrogen bromide to provide benzhydrylthiocarboxamidine bromide, b) reacting haloacetamide with the product of step a) to provide benzhydrylthioacetamide and c) oxidizing the product of step b) to obtain benzhydrylsulphinylacetamide wherein the reaction of step b) is conducted in a solvent comprising a water miscible organic solvent such an alcohol and water in the presence of a basic salt such as an alkali metal hydroxide. This disclosure anticipates the subject-matter of the above-mentioned claims, which is therefore not novel.

Inventive step

7. The subject-matter of claims 4, 5, 10 and 11 cannot be considered to involve an inventive step in the sense of Art. 33(3) PCT. Dependent claims 4, 5, 10 and 11 do not contain any feature which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step. These claims could only be accepted in combination with a novel and inventive main claim.

Further comments

8. It is clear from the description on pages 3, 4, 6 and the examples that the following features are essential to the definition of the invention:

   (1) the temperature at which benzhydrol reacts with thiourea in the presence of hydrogen bromide: 90°C,

(2) the water miscible organic solvent used in the reaction between haloacetamide and benzhydrylthiocarboxamidine bromide, DMF, in the examples,

(3) the ratio of water miscible organic solvent/water: from 9/1 to 1/9,

(4) the specific basic salt used in the production of benzhydrylthioacetamide.

Since independent claim 1 does not contain these features, it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

9. Document D1 could become very relevant to assess the patentability of the present application when it enters the national/regional phase. No check has been made as to whether the priority of the present application and/or the priority of the prior application have been validly claimed.

10. The use of the word "about", especially in connection with numerical ranges, is generally regarded as rendering the determination of the exact scope of the range difficult. When used in a claim as well as in the description, this results in lack of clarity, contrary to Art. 6 PCT. Hence, claims 6-13 and the description should have been drafted without using this word.

11. The term "lower" alcohol used in claim 12 as well as in the description has no generally accepted meaning in the art and is regarded as unclear, since the higher limit of carbon atoms is not unambiguously defined (Art. 6 PCT). Claim 12 and the description should therefore have been drafted including the specific alcohols which fall under this definition.

12. The terms "and the like" used in the description render unclear the scope of the protection sought, contrary to Art. 6 PCT.

13. The terms "substantially" and "approximately" used in the description render unclear the scope of the protection sought, contrary to Art. 6 PCT.

14. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art

disclosed in the documents D1 and D3 is not mentioned in the description, nor are these documents identified therein.

15. The last paragraph in the description is vague and imprecise and implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them.

16. When filing amended claims the applicant should at the same time bring the description into conformity with the amended claims.

17. In order to facilitate the examination of the conformity of the amended application with the requirements of Article 19 (2) and 34 (2) b) PCT, the applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based.

If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.